

**REMARKS**

Applicants believe that the present application is now in condition for allowance.  
Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date \_\_\_\_\_

By \_\_\_\_\_

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. \_\_\_\_\_ for any such fees; and applicant(s) hereby petition for any needed extension of time.

**MARKED UP VERSION ATTACHED TO AMENDMENT IN**

**SERIAL NO. 09/881,050**

**Marked up version of the paragraph on page 1, lines 10-11, is below:**

Fig. 1 shows the nucleotide sequence (SEQ ID NO: 15) of human interferon-beta-2, including 5' and 3' sequences.

**Marked up version of the paragraph on page 1, lines 12-15, is below:**

Fig. 2 shows the amino acid sequence (SEQ ID NO: 16) of human interferon-beta-2. The translation of the open reading frame for IFN- $\beta$ 2 is shown. The signal sequence is shown italicized and the two potential N-glycosylation sites as well as the cysteines capable of forming a disulfide bond are shown underlined and in bold font.

**Marked up version of the paragraph on page 1, lines 21-22, is below:**

Fig. 4 is a protein alignment comparing human interferon-beta-2 (SEQ ID NO: 16) to other interferon types (SEQ ID NOS 17-30).

**Marked up version of the paragraph on page 2, line 5, is below:**

Fig. 12 is a 5' genomic nucleotide sequence (residues 1-394 of SEQ ID NO: 15) of human IFN- $\beta$ 2.

**Marked up version of the paragraph on page 2, line 6, is below:**

Fig. 13 is a nucleotide sequence (residues 395-648 of SEQ ID NO: 15) coding for a 5' region of human IFN- $\beta$ 2.

**Marked up version of the paragraph on page 2, line 7, is below:**

Fig. 14 is a 5' polypeptide sequence (residues 1-69 of SEQ ID NO: 16) of human IFN- $\beta$ 2.

**Marked up version of the paragraph on page 5, lines 1-24, is below:**

Other homologs of IFN- $\beta$ 2's of the present invention can be obtained from mammalian and non-mammalian sources according to

various methods. For example, hybridization with oligonucleotides (e.g., primers to amplify the coding region -5' ATG ATT ATC AAG CAC TTC TTT GGA-3' (SEQ ID NO: 1) and 5'-CTA CCT CGG GCT TCT AAA CTC TGT-3' (SEQ ID NO: 2)). Primers used for expression in E. coli - 5'GGA ATT CCT ACT ACC TCG GGC TTC TAA-3' (SEQ ID NO: 3) and 5'-GCG CGC GCATAT GCT AGA TTT GAA ACT GAT TAT-3' (SEQ ID NO: 4). Primers for the full length known sequence including 5' and 3' untranslated genomic sequence -5'-TTT AGG TGA CAC TAT AGA AT-3' (SEQ ID NO: 5) and 5'-TAA AAT GGA TAG AAT ATA TAA-3' (SEQ ID NO: 6) - can be employed to select homologs, e.g., as described in Sambrook et al., Molecular Cloning, Chapter 11, 1989. Such homologs can have varying amounts of nucleotide and amino acid sequence identity and similarity to IFN- $\beta$ 2. Mammalian organisms include, e.g., rodent, mouse, rat, hamster, monkey, ape, pig, cow, horse, dog, cat, etc. Non-mammalian organisms include, e.g., vertebrates, invertebrates, zebra fish, chicken, Drosophila, C. elegans, Xenopus, yeast such as S. pombe, S. cerevisiae, roundworms, prokaryotes, plants, Arabidopsis, Crustacea, artemia, viruses, etc. To select oligonucleotides for hybridization an effective method can be used. For example, IFN- $\beta$ 2-specific regions can be identified by comparing and IFN-B-2 of the present invention with other IFN- $\beta$ 2 types and selecting those amino acid sequences which only appear in the former (i.e., non-conserved, or, "specific-for" IFN- $\beta$ 2). See Fig.4 showing conserved and non-conserved regions between the different interferon types. Non-conserved amino acid sequences can be chosen (e.g., KSLSP (SEQ ID NO: 9)) and degenerate probes can be designed based on such sequences. See, also, Venkataraman et al., Proc. Natl. Acad. Sci., 96:3658-3663, 1999. Other specific (i.e., non-conserved) and/or conserved amino acid sequences can be found routinely e.g., by searching a gene/protein database using the BLAST set of computer programs.

**Marked up version of the paragraph on page 5, lines 25-31 thru page 6, lines 1-3, is below:**

The invention also relates to IFN- $\beta$ 2-specific amino acid sequences, e.g., a defined amino acid sequence which is found in the

particular sequence of Figs. 2 and 4, but not in other interferon types. Preferred polypeptides are at least about eight contiguous amino acids, e.g., about 9, 10, 12, 15, 20, 21, 22, 25, 30, 40, 50, etc. Such polypeptides can comprise, e.g., KHFFGTV (SEQ ID NO: 7), IIFQQRQV (SEQ ID NO: 8), KSLSP (SEQ ID NO: 9), FRANI (SEQ ID NO: 10), AEKLSGT (SEQ ID NO: 11), CLFFVFS (SEQ ID NO: 12), QGRPLNDMKQELTTEFRSPR (SEQ ID NO: 13), and fragments thereof. An IFN- $\beta$ 2-specific amino acid sequence or motif can be useful to produce peptides as antigens to generate an immune response specific for it. Antibodies obtained by such immunization can be used as a specific probe for a mammalian IFN- $\beta$ 2 protein for diagnostic or research purposes, including as expression markers.

**Marked up version of the paragraph on page 16, lines 25-31 thru page 7, lines 1-12, is below:**

Another aspect of the present invention is a nucleotide sequence which is unique to a mammalian IFN- $\beta$ 2. By a unique sequence to an IFN- $\beta$ 2, it is meant a defined order of nucleotides which occurs in IFN- $\beta$ 2, e.g., in the nucleotide sequences of Fig 1, but rarely or infrequently in other nucleic acids, especially not in an animal nucleic acid, preferably mammal, such as human, rat, mouse, etc. Unique nucleotide sequences include the sequences, or complements thereto, coding for amino acids KHFFGTV (SEQ ID NO: 7), IIFQQRQV (SEQ ID NO: 8), KSLSP (SEQ ID NO: 9), FRANI (SEQ ID NO: 10), AEKLSGT (SEQ ID NO: 11), CLFFVFS (SEQ ID NO: 12), QGRPLNDMKQELTTEFRSPR (SEQ ID NO: 13), and fragments thereof as shown in Fig. 1. Such sequences can be used as probes in any of the methods described herein or incorporated by reference. Both sense and antisense nucleotide sequences are included. A unique acid according to the present invention can be determined routinely. A nucleic acid comprising such a unique sequence can be used as a hybridization probe to identify the presence of, e.g., human or mouse IFN- $\beta$ 2, in a sample comprising a mixture of nucleic acids, e.g., on a Northern blot. Hybridization can be preformed under high stringent conditions (see above) to select nucleic acids (and their

complements which can contain the coding sequence) having at least 95% identity (i.e., complementarity) to the probe, but less stringent conditions can also be used. A unique IFN- $\beta$ 2 nucleotide sequence can also be fused in-frame, at either its 5' or 3' end, to various nucleotide sequences as mentioned throughout the patent, including coding sequences for other parts of IFN- $\beta$ 2, enzymes, GFP, etc, expression control sequences, etc.